# Targeting Angiogenesis and Growth Factor Pathways: Implications for Cancer Therapy and Tumor Microenvironment Regulation

Ibrahim D. Al deeb[1*], Enas M. Daoud[1]

## Abstract

Angiogenesis is a critical process in tumor development, involving the formation of new blood vessels from pre-existing ones. Tumor vasculature, unlike normal vasculature, exhibits structural abnormalities, including leaky and poorly organized vessels. These features create a hypoxic and acidic microenvironment, significantly impacting the efficacy of chemotherapeutic interventions and altering endothelial cell physiology. This review synthesizes recent findings on the roles of endothelial cells and tumor vasculature in angiogenesis. It highlights key mechanisms such as endothelial cell migration, proliferation, and the involvement of angiogenic regulators like vascular endothelial growth factor receptor-2 (VEGFR-2) and Delta-like ligand 4 (Dll4)/NOTCH signaling pathways. Endothelial cells play pivotal roles in vascular sprouting, tube formation, and stabilization during angiogenesis. Activation of VEGFR-2 by vascular endothelial growth factor (VEGF) determines endothelial cell fate, orchestrating tip and stalk cell differentiation through Dll4/NOTCH signaling. Additionally, tumor vasculature abnormalities, such as deficient pericyte coverage and elevated interstitial pressure, create challenges for effective drug delivery and promote tumor progression. Despite significant progress in understanding angiogenesis, several unanswered questions remain. Key challenges include identifying the most impactful angiogenic factors, understanding their regulatory mechanisms, and determining whether targeting tumor cells, stromal cells, or endothelial cells is most effective. The interplay between angiogenic factors suggests a complex network that requires further exploration to unravel tumor pathogenesis. Targeting angiogenesis holds promise as a therapeutic strategy. However, the current focus on VEGF pathways has limited the development of alternative anti-angiogenic agents. Future research should prioritize the discovery of novel angiogenic regulators and their interactions to expand therapeutic options.

**Keywords:** Angiogenesis, Tumor Vasculature, Endothelial Cells, Vegfr-2, Dll4/Notch Signaling, Hypoxic Microenvironment, Anti-Angiogenic Therapy

***Significance*** | Exploring angiogenesis and growth factor signaling advances understanding of cancer biology, offering novel therapeutic strategies for effective tumor management.

*Correspondence. Ibrahim D. Al deeb, Pharmacological and Diagnostic Research Centre, Faculty of Pharmacy, Al-Ahliyya Amman University, Amman 19328, Jordan.
E-mail: i.aldeeb@ammanu.edu.jo

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## 1. Introduction

### *1.1 Angiogenesis*

Angiogenesis, the formation of new blood vessels from pre-existing ones, plays a crucial role in both physiological tissue maintenance and pathological conditions such as tumor development. It involves a complex cascade of events, including extracellular matrix remodeling, endothelial cell migration, proliferation, differentiation into capillaries, and vascular anastomosis (Blood & Zetter, 1990). Tumor angiogenesis supports tumor progression by supplying oxygen and nutrients to the growing mass and facilitating

**Author Affiliation.**
[1] Pharmacological and Diagnostic Research Centre, Faculty of Pharmacy, Al-Ahliyya Amman University, Amman 19328, Jordan.

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metastasis by enabling tumor cells to spread to distant organs (Carmeliet & Jain, 2000; Ferrara, 2010).

### *1.2 Physiological and Pathological Angiogenesis*

During embryogenesis, new blood vessel formation involves vasculogenesis (endothelial cell proliferation and arrangement into tubes) and angiogenesis (sprouting from existing vessels). After morphogenesis, blood vessels become largely quiescent. In adults, angiogenesis is transiently activated during specific physiological processes like wound healing and the female reproductive cycle. This activity is tightly regulated by endogenous inhibitors such as thrombospondin-1, angiostatin, and endostatin, which ensure controlled angiogenesis (Seppinen et al., 2008). These inhibitors act as intrinsic barriers against tumor-induced angiogenesis or mediate transient responses for tissue repair and remodeling.

Conversely, during tumor progression, angiogenesis remains persistently activated, enabling continuous blood vessel sprouting to support tumor growth (Hanahan & Folkman, 1996).

## *2 Cancer Angiogenesis*

### *2.1 Types of Angiogenesis*

Tumors employ multiple strategies to secure their blood supply, including sprouting angiogenesis, vessel co-option, intussusception, and mobilization of bone marrow-derived endothelial progenitor cells (Rafii et al., 2002; Adams & Alitalo, 2007).

**Vessel Co-option**: Tumor cells grow along pre-existing vessels and extract nutrients directly without inducing new vessel formation. This is commonly observed in metastases (Holash et al., 1999).

**Intussusception**: Existing vessels split longitudinally to increase vascular density without endothelial cell proliferation, making it a rapid mechanism for vascular remodeling.

**Sprouting Angiogenesis**: This slower process involves forming new vessels from existing ones to reach avascular regions (Figure 1). Proteases degrade the extracellular matrix, allowing endothelial cells to migrate and proliferate. These cells eventually join pre-existing vessels, form lumens, and recruit pericytes to stabilize the new vessels (Ribatti & Crivellato, 2012). Sprouting is triggered by hypoxia, which induces the release of pro-angiogenic factors such as vascular endothelial growth factor (VEGF). Tip cells, responding to VEGF, guide new vessel growth, while stalk cells proliferate and extend the sprout. Cytoskeletal rearrangements in stalk cells give the vessels their tubular shape, influenced partly by hydrodynamic forces (Gebala et al., 2016; Charpentier & Conlon, 2014).

### *2.2 Regulation of Angiogenesis via VEGF/VEGFR Pathway*

The angiogenesis process is tightly regulated by a balance of pro-angiogenic factors, including VEGF, basic fibroblast growth factor (FGF), and interleukin-8 (IL-8), and anti-angiogenic factors. Tumor and stromal cells release these factors to modulate endothelial cell activity and drive angiogenesis (Ferrara, 2010).

VEGF is a critical regulator of angiogenesis and endothelial mitogenesis. Elevated VEGF levels are associated with poor prognosis in various human cancers. The VEGF family comprises VEGF-A through VEGF-E and placental growth factors (PIGF)-1 and -2, with VEGF-A being the most potent pro-angiogenic factor (Dvorak et al., 1995). VEGF-A binds to tyrosine kinase receptors VEGFR-1 and VEGFR-2, with VEGFR-2 mediating stronger pro-angiogenic signaling (Gille et al., 2001). Hypoxia-inducible factor-1α (HIF-1α), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF) upregulate VEGF expression under hypoxic conditions (Reinmuth et al., 2001; Petit et al., 1997).

VEGFR-1 and VEGFR-2 are type III tyrosine kinase receptors (Shibuya & Claesson-Welsh, 2006). VEGF binding induces receptor dimerization and phosphorylation, activating downstream signaling pathways that promote endothelial cell proliferation, migration, survival, and capillary tube formation (Olsson et al., 2006; Holmqvist et al., 2004). Inhibiting VEGF-VEGFR-2 interactions prevents the phosphorylation of downstream kinases, leading to reduced activity of extracellular signal-regulated kinase (ERK), phosphorylated Akt (p-Akt), focal adhesion kinase (FAK), and mitogen-activated protein kinase (MAPK) (Rathinavelu et al., 2017). This disruption impairs the survival and proliferation of both endothelial and cancer cells.

By targeting VEGF/VEGFR signaling, anti-angiogenic therapies aim to restrict tumor vascularization, thereby starving the tumor of oxygen and nutrients necessary for growth and metastasis. Understanding these mechanisms offers a foundation for developing novel therapeutic strategies against cancer.

### *2.3 Other Angiogenesis Regulatory Pathways*

#### *2.3.1 Alternative Pro-Angiogenic Factors*

##### *2.3.1.1 Platelet-Derived Growth Factor (PDGF)*

PDGF and its receptor (PDGFR) play essential roles in blood vessel maturation and the recruitment of pericytes (Lindahl et al., 1997). Released by endothelial cells, PDGF acts in a paracrine manner to activate PDGFR, which has tyrosine kinase activity. PDGFR exists in two forms, PDGFR-α and PDGFR-β, primarily expressed by pericytes and smooth muscle cells to facilitate vascular development (Andrae et al., 2008). The overexpression of PDGFR has been associated with poor prognoses in ovarian cancer, suggesting a critical role for the PDGF pathway in human cancers (Dabrow et al., 1998).

##### *2.3.1.2 Fibroblast Growth Factor (FGF)*

Among the earliest discovered angiogenic factors, FGF ligands stimulate endothelial cell proliferation, migration, and differentiation (Abraham et al., 1986). FGFs demonstrate high affinity for heparan sulfate proteoglycans, which act as co-receptors by binding FGF ligands and one of the four FGFRs (Korc & Friesel, 2009). With tyrosine kinase activity, FGFRs are expressed across various cell types, including endothelial cells, contributing to robust

**Table** 1. Angiogenic Regulators. Normal Angiogenic Process Is Highly Regulated Through Balance Between Angiogenic Inducers and Inhibitors. Any Dysregulation of This Balance Toward Angiogenic Inducers Will Lead to Uncontrolled Angiogenesis Such as Tumor Angiogenesis.

| Angiogenic Inducers | Mechanisms | Reference | Angiogenic Inhibitors | Mechanisms | Reference |
|---|---|---|---|---|---|
| VEGFA, B, C, D and receptors VEGFR-2 and neuropilin-1 | Increase endothelial cells permeability, proliferation, and survival | Rathinavelu et al. (2017) | TSP-1, -2 | Inhibits endothelial cells migration, proliferation, adhesion, and survival | Seppinen et al. (2008) |
| FGF-1 and -2 | Induce endothelial cells, smooth muscle cells, and fibroblasts proliferation and differentiation | De Luca et al. (2008) | Angiostatin | Inhibits endothelial cells migration, proliferation, adhesion, and survival | Seppinen et al. (2008) |
| PDGF and PDGFR | Recruit pericytes and smooth muscle cells | Andrae et al. (2008) | Endostatin | Inhibits endothelial cells migration, proliferation, adhesion, and survival | Seppinen et al. (2008) |
| Ang | Regulates blood vessels | Augustin et al. (2009) | IL-4, -12, -18 | Downregulates FGF | Doyle et al. (2014) |
| TGF-α and TGF-α receptor | Enhance extracellular matrix production | Bernabeu et al. (2009) | Tumstatin and canstatin (fragments of collagen IV) | Inhibits endothelial cells migration, proliferation, and pathways like PI3K, mTOR, and FAK | Kamphaus et al. (2000), Eikesdal et al. (2008) |
| Integrins | Facilitate binding to matrix macromolecules and proteinases | Mitra and Schlaepfer (2006) | Arrestin | Inhibit cell cycle and induce apoptosis | Rosca et al. (2011) |
| VE-cadherins | Enhance endothelial cells junctions | Gavard and Gutkind (2006) | Vascular endothelial growth inhibitor (VEGI) | Inhibits endothelial cells proliferation and migration | Hou et al. (2005) |
| Matrix metalloproteinases (MMPs) | Degrades blood vessels wall and extracellular matrix | Adams and Alitalo (2007) | Soluble VEGFR | Trap receptor for VEGF and PIGF | Lähteenvuo et al. (2009) |
| Endothelial nitric oxide synthetase (eNOS) and cyclooxygenase-2 (COX-2) | Generate NO inside cells and increase expression of VEGF | Kevil et al. (2005) | Interferons -α, -β, -γ | Inhibits endothelial cells migration | Ferrara et al. (2010) |
| Cytokines, chemokines (IL-1, IL-8) | Induce chemotaxis in endothelial cells | Adams and Alitalo (2007) | Ang-2 | Antagonist to Ang-1 | Winkler et al. (2004) |

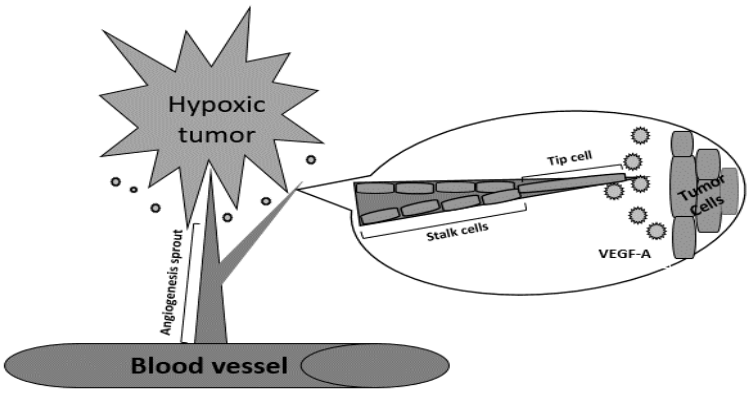


**Figure 1.** Sprouting Angiogenesis. As tumor grows and more oxygen is needed, a hypoxic situation will be created inside the tumor cells, triggering release of pro-angiogenic factors such as VEGF. Consequently, resulting in migration of tip-cells toward VEGF gradient that lead stalk-cells behind. The stalk-cells will proliferate to generate the extension of sprouting angiogenesis as well as forming vessel lumen upon cytoskeletal rearrangement.

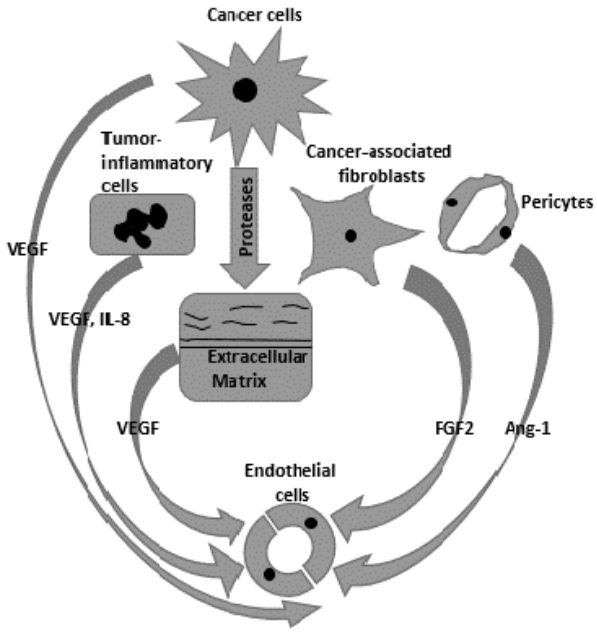


**Figure 2.** Tumor cells are not the only factor that regulates endothelial cells. Other cells that participate in angiogenesis regulation, such as cancer-associated fibroblasts which release FGF-2; pericytes which release Ang-1 and help in blood vessels maturation; extra growth factors released from extracellular matrix degradation due to proteases activity; and other inflammatory cells which release VEGF and proteases during their activity.

angiogenic activity (Lindner et al., 1990). Overexpression of FGF ligands, particularly FGF-2, or FGFRs is documented in multiple human cancers, correlating with poor outcomes in conditions like non-small cell lung cancer and bladder carcinoma (Gazzaniga et al., 1999).

#### *2.3.1.3 Epidermal Growth Factor (EGF)*

EGF binds to epidermal growth factor receptors (EGFRs), most of which exhibit tyrosine kinase activity, except HER3. This interaction promotes metastasis, angiogenesis, cell proliferation, migration, adhesion, and differentiation (Yarden & Sliwkowski, 2001). Activation of the EGFR pathway indirectly regulates angiogenesis by upregulating the release of pro-angiogenic factors such as VEGF. Consequently, while EGF/EGFR pathways influence angiogenesis, their role is secondary to other pathways, including VEGF and PDGF systems (De Luca et al., 2008).

#### *2.3.1.4 Transforming Growth Factor-β (TGF-β)*

TGF-β and its receptors, expressed by various cell types, are integral to angiogenesis, cell differentiation, wound healing, and growth inhibition (Blobe et al., 2000). Depending on its concentration, TGF-β exhibits pro- and anti-angiogenic properties. Low levels contribute to angiogenesis and protease production, whereas high levels inhibit endothelial cell growth (Carmeliet, 2003). Tumor cells exploit TGF-β's ability to regulate angiogenesis and cell invasion, resisting its inhibitory effects. Overexpression of TGF-β1 has been linked to angiogenesis, metastasis, and poor prognosis in gastric, colon, breast, and other cancers (Bernabeu et al., 2009; Bierie & Moses, 2006). TGF-β receptors possess serine/threonine kinase domains (except TGF-β3) and activate pathways such as SMADs, MAPK, and PI3K upon stimulation (Blobe et al., 2000; Bierie & Moses, 2006).

#### *2.3.1.5 Angiopoietins and the Tie Receptor (Ang/Tie)*

The Ang/Tie system regulates vascular development and angiogenesis, with Ang family ligands (Ang-1, Ang-2, Ang-3, and Ang-4) binding to the Tie-2 receptor (Augustin et al., 2009). Ang-1, through Tie-2, promotes vascular maturation and normalization, exhibiting anti-tumor effects, although some studies suggest tumor growth stimulation (Winkler et al., 2004). Ang-2 displays context-dependent effects: in the presence of VEGF, it promotes angiogenesis, while in its absence, it induces vessel regression (Augustin et al., 2009). Targeting Ang-2 in preclinical studies has shown promising results, inhibiting tumor growth and endothelial cell proliferation, highlighting the potential of Ang/Tie pathway inhibition for anti-angiogenic therapies (Oliner et al., 2004).

Table 1 summarizes key angiogenic inducers and inhibitors, along with their proposed mechanisms of action (see Table 1).

### *2.3.2. Hypoxic Pathway*

Oxygen levels are critical regulators of the synthesis and secretion of growth factors and inflammatory mediators within tissues. Hypoxia in tumors stimulates the expression of several growth factors, notably vascular endothelial growth factor (VEGF), through the transcription factor hypoxia-inducible factor 1-alpha (HIF-1α) (Terzuoli et al., 2010). Under normoxic conditions, HIF is degraded and remains inactive, whereas hypoxic conditions stabilize and activate HIF, leading to the transcription of target genes. In addition to hypoxia, other factors can also activate and enhance HIF expression. These include growth factors and cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), epidermal growth factor (EGF), and insulin-like growth factor-1 (Stiehl et al., 2002; Jiang et al., 2001; Fukuda et al., 2002; Hellwig-Bürgel et al., 1999).

Oncogenes also play a role in triggering HIF expression and activity. For instance, mutant Ras enhances angiogenesis by upregulating VEGF expression via activated HIF (Rak et al., 1995). Similarly, oncogenes such as V-Src, HER2, and activated pathways like PI3K and MAPK have been associated with increased HIF activity or expression (Jiang et al., 1997; Laughner et al., 2001; Blancher et al., 2001).

### *2.3.3. Inflammatory Pathway*

Angiogenesis and inflammation are interconnected processes that support tumor growth and progression (Albini et al., 2012). Chronic inflammation has been implicated in tumor initiation and pathological angiogenesis due to complex interactions between immune, tumor, and endothelial cells (Carmeliet & Jain, 2011). When cells experience stress or damage—such as during infection—they express endogenous molecules known as damage-associated molecular patterns (DAMPs), which are detected primarily by leukocytes (Nguyen et al., 2017). This interaction amplifies inflammation by activating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, which drives the release of pro-inflammatory cytokines and chemokines, including VEGF, IL-1α, IL-1β, TNF-α, IL-8, macrophage inflammatory protein-1 alpha (MIP-1α), and RANTES (Afonina et al., 2017).

These cytokines target endothelial cells, leading to vascular hyperpermeability, vasodilation, and increased expression of adhesion molecules such as E-selectin, P-selectin, ICAM-1, ICAM-2, and VCAM-1. This, in turn, alters cell-cell junctions, exacerbates inflammation, and promotes angiogenesis (De Palma et al., 2017). Dysregulated inflammation activates survival signaling pathways in tumor cells, resulting in the release of angiogenic factors such as fibroblast growth factor-2 (FGF-2), CXCL8, WNT7b, ANGPT-2, IL-1β, IL-6, IFN-α, CXCL9/10, and matrix metalloproteinases (MMPs) 2/9 (Hanahan & Weinberg, 2011). Targeting inflammatory mediators and associated angiogenic molecules may improve tumor treatment (Hanahan & Weinberg, 2011).

### *2.3.4. Oxidative Stress Pathway*

Reactive oxygen species (ROS) are known inducers of angiogenesis through the upregulation of VEGF, VEGFR-2, angiopoietin-1

(Ang-1), and Tie-2 expression (Colavitti et al., 2002). ROS, primarily originating from mitochondria, regulate innate immune responses through two mechanisms: direct activation of inflammatory mediators and upregulation of redox-sensitive transcription factors such as NF-κB (Colavitti et al., 2002). NF-κB activation leads to the expression of genes encoding inflammatory cytokines, adhesion molecules, enzymes, and angiogenic factors (Afonina et al., 2017). Consequently, targeting NF-κB can block macrophage and endothelial recruitment, downregulate ICAM expression, and indirectly inhibit angiogenesis (Hanahan & Weinberg, 2011).

#### *2.3.5. Downstream Signaling Pathway*

VEGFR-2 is the primary tyrosine kinase receptor mediating VEGF-induced angiogenesis through several signaling pathways, including PLCγ-PKC-Raf kinase-MEK-MAPK, PI3K-Akt-mTOR, and Src tyrosine kinases. These pathways regulate endothelial cell migration, invasion, adhesion, and survival (Mitra & Schlaepfer, 2006). Dysregulation of VEGFR-2 or other tyrosine kinase receptors can occur via amplification or overexpression, gain-of-function mutations, genomic translocations, or persistent stimulation by pro-angiogenic factors (Afonina et al., 2017). This dysregulation activates downstream signaling pathways, ultimately determining receptor activation's biological outcomes.

#### *2.3.6. Cell Surface-Associated Proteins Pathway*

Endothelial cell adhesion molecules have a critical role in angiogenesis. Diseases such as atherosclerosis and diabetic retinopathy have been associated with increased adhesion molecule expression and neovascularization (Jablonska et al., 2010). Soluble forms of E-selectin, VCAM-1, and ICAM-1 have also been implicated in angiogenesis through unidentified mechanisms (Kevil et al., 2004).

During vascular sprouting, stromal-derived factor-1 (CXCL12) and CCL2 are pivotal in guiding endothelial cell invasion, migration, and survival (Lähteenvuo et al., 2009). Additionally, the transcription level of platelet endothelial cell adhesion molecule-1 (PECAM-1) is essential for cell migration (Kevil et al., 2004). Targeting the interaction between CXCL12 and PECAM-1 offers a potential approach to inhibit tumor angiogenesis (Lähteenvuo et al., 2009). Moreover, blocking TNF-α can prevent monocyte adhesion to the endothelial cell monolayer, thereby inhibiting inflammatory angiogenesis (Hou et al., 2005).

Activation of VEGFR-2 stimulates the vascular endothelial (VE)-cadherin pathway, resulting in strong cell-cell junctions and adherens junction openings, which induce endothelial permeability (Gavard & Gutkind, 2006). These interactions between endothelial, tumor, and stromal cells underscore the complexity of angiogenesis regulation in tumors (Figure 2).

## 3. Role of Endothelial Cells and Tumor Vasculature Environment in Angiogenesis

Tumor vasculature significantly differs from normal vessels. Tumor blood vessels are characterized by leakage, abnormal architecture, lack of pericyte coverage, and disorganized arrangements of arterioles, capillaries, and venules (Baluk et al., 2005). Additionally, the absence of lymphatic vessels and poor perfusion elevate interstitial pressure within tumors, impeding the delivery of chemotherapeutic agents (Duda et al., 2007). These factors create hypoxic and acidic tumor environments, which profoundly influence the physiology, morphology, and gene expression of tumor endothelial cells (Helmlinger et al., 1997).

Endothelial cells lining the lumen of blood vessels play a crucial role in angiogenesis. These cells undergo significant mechanical and physiological changes during vascular sprouting (Ausprunk & Folkman, 1977), stalk cell proliferation (Keegan et al., 1982), tip cell migration (Zetter, 1980), tube formation (Folkman & Haudenschild, 1980), and vascular stabilization (Baluk et al., 2003). The process involves cytoskeletal rearrangement (Cao et al., 2017), focal adhesion formation (Abedi & Zachary, 1997), and contractile force generation (Hu et al., 2016).

Activation of the VEGFR-2 receptor by VEGF determines the fate of endothelial cells as either tip or stalk cells through the Delta-like ligand 4 (Dll4)/Notch1 signaling pathway (Simons et al., 2016). When VEGF binds to VEGFR-2, it triggers intracellular kinase activity that initiates cascades resulting in tip cell selection. Tip cells express the Dll4 ligand on their surface, which binds to the Notch1 receptor on adjacent endothelial cells. This interaction reduces the neighboring cell's sensitivity to VEGF, directing it toward stalk cell proliferation (Hellström et al., 2007; Blanco & Gerhardt, 2013).

## 4. Conclusion

In summary, angiogenesis is a complex process essential for tumor growth and involves extracellular matrix degradation, endothelial cell migration and proliferation, tube formation, and vessel maturation. These processes recruit both tumor and stromal cells, highlighting the intricate interplay between cellular and molecular mechanisms.

Over the years, numerous angiogenic regulators have been identified. Despite these advancements, critical questions remain unanswered. For instance, which angiogenic factors have the most significant impact on angiogenesis? Are these regulators governed by a single mechanism that initiates angiogenesis? Should therapeutic targets focus on tumor-derived, endothelial, or stromal cell-initiated regulators—or all simultaneously? Moreover, do the patterns of angiogenic factors vary across different malignancies? It is evident that angiogenic regulators function within a network of interactions, necessitating a deeper understanding of these relationships for comprehensive insights into pathogenesis.

The discovery of novel angiogenic regulators could pave the way for innovative therapeutic strategies. To date, most angiogenesis-targeting therapies focus on the VEGF signaling pathway, leaving room for the development of alternative anti-angiogenic agents targeting other pathways.

## Author contributions

I.D.A. conceptualized and supervised the study, contributed to data analysis, and finalized the manuscript. E.M.D. conducted the literature review, performed data collection, and contributed to manuscript drafting and editing. Both authors read and approved the final manuscript.

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## Competing financial interests

The authors have no conflict of interest.

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